REVIEW

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Physical Activity Modulating Lipid Metabolism in Gallbladder Diseases

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ABSTRACT

Physical activity encompasses a series of overall benefits on cardiovascular health and metabolic disorders. Research has recently focused on the hepatobiliary tract, as an additional target of the health-related outcomes of different types of physical exercise. Here, we focus on the global features of physical activity with respect to exercise modality and intensity, and on studies linking physical activity to lipid metabolism, gallbladder diseases (gallstones, symptoms, complications and health-related quality of life), gallbladder motor-function, enterohepatic circulation of bile acids, and systemic metabolic inflammation. Additional studies need to unravel the pathophysiological mechanisms involved in both beneficial and harmful effects of physical activity in populations with different metabolic conditions.

Key words: bile acids – gallbladder disease – lipids – physical activity.

Abbreviations: BA: bile acid; BMI: body mass index; CVD: cardiovascular disease; HDL: high-density lipoprotein; HRQoL: health-related quality of life; LDL: low-density lipoprotein; MET: metabolic equivalent task; T2D: type 2 diabetes.

INTRODUCTION

The majority of the elderly population suffers from several chronic diseases [1]. Sedentary lifestyles certainly play a major role in this respect [2], and contribute to negative effects on quality of life [3], the cardiovascular system, and overall health status [4]. Lack of physical exercise contributes to the rise of non-communicable diseases such as obesity, type 2 diabetes (T2D), cardiovascular disease (CVD), and premature mortality in the long-term [5]. This unfavorable condition already starts during childhood and adolescence [6]. By contrast, regular physical activity, along with healthy lifestyles, reduces the risk of CVD [5], providing beneficial effects on various chronic diseases [2], including obesity and T2D, the main components of the metabolic syndrome. The benefits of physical activity might extend to dyslipidemia and to the hepatobiliary tract, i.e., gallbladder and cholesterol cholelithiasis [7-9], one of the "fellow travelers" with the metabolic syndrome [8, 10].

In this paper, we focus on the mechanisms linking physical activity to lipid metabolism and pathophysiological mechanisms of gallbladder diseases.

GLOBAL FEATURES OF PHYSICAL ACTIVITY

Physical activity is a sustained body movement, generating an increased energy expenditure [11]. Planned, regularly, repeated and intentional physical exercise maintains health and fitness (Table I) [11, 12]. Aerobic capacity is a regular activity allowing vigorous tasks without undue fatigue and can be related to general health (muscular endurance, mobility, muscular strength, body composition) or to skill improvement (balance, agility, power, coordination, reaction time) [11].

Determination of exercise intensity relies on the calculation of specific parameters. Monitoring of physical activity is based on metabolic equivalent tasks (METs), which is representative of the volume of oxygen (VO_2) consumed during a certain physical activity (one MET=3.5 mL/kg/min) [11, 13]. A MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest, i.e., 1 MET is the rate of

Table I. Different effects of physical activity by exercise modality.

Exercise modality	Examples	Effects
Aerobic exercise	- Walking - Running	Favours endurance and increases cardiovascular and respiratory fitness
Strength exercise	- Weight lifting - Bodyweight resistance	Helps increase muscular resistance and strength
Balance exercise	- Tai chi - Heel-toe walking	Improves balance, proprioception and prevents falls
Mobility exercise	- Yoga - Stretching	Maintains and improves joint motions and increases muscle lengthening

energy expenditure while at rest. A 5 METs activity therefore is equal to 5 times the energy used at rest. Thus, performing a 5 METs activity for 60 minutes, means 5 x 60 = 300 MET-minutes or 5 METs/hour of physical activity. Scientifically, 500 to 1000 MET-minutes total weekly physical activity produces substantial health benefits for adults, and there is a dose-response beneficial effect already starting below 500 .The intensity of aerobic physical activity can be better classified into three absolute groups, also according to US Department of Health and Human Services, 2008 Physical Activity Guidelines for Americans (https://health.gov/paguidelines/2008/pdf/paguide.pdf) [14, 15]:

- Light-intensity activities are defined as 1.1 to 2.9 METs;
- Moderate-intensity activities are defined as 3.0 to 5.9 METs;
- Vigorous-intensity activities are defined as 6.0 METs or more.

In this respect, walking at 5.3 km per hour requires 3.3 METs of energy expenditure (i.e. moderate-intensity activity), while running at 9.6 km per hour is a 10 METs activity (i.e., vigorous-intensity activity).

In contrast to unmodifiable risk factors such as genetics, age, and gender, physical inactivity is a modifiable risk factor. Clinicians should prescribe daily physical activity of at least 30 min duration to all subjects, as part of a well-structured lifestyle program. Even moderate-intensity exercise brings beneficial health effects [11]. Recent physical activity guidelines for adults from USA, Canada, Australia and Europe recommend at least 150 min/week of moderate-intensity exercise, such as brisk walking, or at least 75 min/week of vigorous-intensity exercise, such as heavy weightlifting [16-20]. It is a fact that unfit individuals have increased risks of mortality (2-3 times more) when compared to fitter individuals. This alarming trend occurs regardless of body composition or presence of CVD [21].

GENERAL EFFECTS OF PHYSICAL ACTIVITY ON LIPID METABOLISM

A large meta-analysis showed that physical activity holds several beneficial effects on lipid metabolism: decreased serum triglycerides and cholesterol [22], and increased in serum high-density lipoprotein (HDL) levels [22-24]. This association is linked particularly to increased aerobic capacity (VO_2peak) [25]. Of note, serum HDL represents a marker of reverse cholesterol transport to liver [26, 27], a step acting as the precursor of bile acid synthesis [28]. In turn, this HDL-mediated pathway could participate in mechanisms leading to decreased biliary cholesterol saturation [27]. In line with this possibility, serum HDL levels are inversely related to gallstone prevalence (see below) [29]. The favorable effects of physical exercise might also extend to the control of the fatty acid-dependent hypersecretion of gallbladder mucin [30, 31], another major factor involved in the pathogenesis of cholesterol cholelithiasis [32-34].

Adolescents performing a higher amount of physical activity have lower body fat composition and more favorable HDL cholesterol [35]. Noteworthy, in the cited study, almost 48% of participants did not meet the daily physical activity recommendations. Also, in pre-adolescent girls, intensity of physical activity is a more important determinant of low-density lipoprotein (LDL)cholesterol than energy spent in exercising [36]. Indeed, in another study in men, physical activity over 9 kcal/minute (i.e., vigorous) was associated with a decreased serum total cholesterol and triglycerides, as well as increased aerobic fitness [37]. Slightly decreased triglycerides and increased HDL cholesterol levels were also observed in Brazilian participants performing vigorous physical activity [38]. Thus, long-term physical activity should be promoted in order to improve the lipid profile of gallstone patients, with special emphasis to the number of steps and intensity of performance, which accelerates fat oxidation in the body [13].

GALLSTONE DISEASE

The prevalence and incidence of cholelithiasis (i.e. the physical presence of solid concrements, stones, in the gallbladder) are rising worldwide. About 20% of adults in developed countries have gallstones [32], with an incidence rate of new cases of 0.6-1.39% per year [39]. About 20 million Americans and 10-15% of adults in Europe suffer from gallbladder disease [32, 40]. Aging is associated with an increasing prevalence of gallstones which remains markedly higher in women than in men [41]. Although gallstones remain asymptomatic, about 20% of gallstone patients will develop symptoms (colicky pain) and/or complications during their lifetime (acute/chronic cholecystitis, cholesterolosis and gallbladder polyps, gallbladder cancer, acute pancreatitis, biliary obstruction, acute cholangitis, biliary enteric fistula and gallstone ileus, choledocholithiasis, or recurrent pyogenic cholangitis) [42, 43]. Such complications are frequently characterized by critical care aspects [10, 44]. Thus, cholelithiasis is still the most common gastroenterological cause of hospital admissions across Europe [45], and the socioeconomic costs of cholelithiasis remain very high. Approximately 75% of gallstones in westernized countries consist mainly of packed cholesterol monohydrate crystals [32, 41, 46-48]. The remaining 25% of gallstones are either black pigment stones in 20% (polymerized calcium bilirubinate) growing in the gallbladder or brown pigment stones in 5% (mostly calcium bilirubinate), growing in the infected extrahepatic or intrahepatic bile ducts [33, 41, 47, 49, 50]. The increasing trends of cholelithiasis parallel the rise in obesity [51, 52], T2D [53-56], insulin resistance [56, 57] and metabolic syndrome [48] worldwide. Additional risk factors

are reduced serum HDL, hypertriglyceridemia [58], sedentary lifestyles [59, 60], hormone replacement therapy [59], and fast-food consumption [59]. Along with obesity, the risk of developing symptomatic gallstones prone to cholecystectomy, is increasing [61-67].

The most important pathogenic factors for cholesterol gallstones are depicted in Fig. 1 and include: a) predisposing genetic factors and lithogenic (LITH) genes [68, 69]; b) hepatic factors leading to the hypersecretion of cholesterol, which in turn promote a sustained supersaturated gallbladder bile [70]; c) rapid phase transition of increased biliary cholesterol, contributing to the precipitation and aggregation of solid cholesterol crystals [71, 72]; d) defective gallbladder motility and immune-mediated inflammation, with hypersecretion of mucin gel by the epithelium and luminal accumulation [73]; e) intestinal factors involving slow transit, increased cholesterol absorption from the small intestine, decreased bile absorption and modified gut microbiota [27, 42, 43] (Fig. 1).

GENERAL EFFECTS OF PHYSICAL ACTIVITY ON THE GALLBLADDER, HEPATOBILIARY TRACT, AND SYSTEMIC PATHWAYS

Physical activity influences gallbladder function and contributes to the reduction of the risk of gallstones and gallstone disease (i.e., symptoms, complications due to the presence of gallstones). The main effects of physical activity on gallbladder and hepatobiliary tract according to population studies appear in Table II. Evidence shows that several mechanisms, also independent on the gallbladder per se, can be involved.

Mechanisms linking the potential beneficial effects of aerobic exercise to gallstone disease include hepatic cholesterol synthesis, absorption and secretion, gallbladder and intestinal motility, and neuro-hormonal pathways [51, 60, 74-77]. In the study of Utter et al. [78], in obese women, significant gallbladder emptying occurred for both exercise (five 45 min brisk walking sessions per week at 75.2±0.5% of maximum heart rate) and control, either pre- or post intervention. The exercise group had increased gallbladder ejection fraction after exercise training (39.5±4.9% to 54.7±6.5%) but this 15.2% increase did not differ from that seen in the controls [78]. American Indians have a high risk of cholesterol gallstones and metabolic disorders. In 3,143 subjects of both sexes, from 13 American Indian communities examined at baseline in 1989-92 and at an ultrasonographic follow-up in 1993 and 1995, the authors found that physical activity was inversely related to the development of gallbladder disease. Outcomes of this study were independent from potential confounders as body mass index (BMI) and sex, but could have been influenced by the presence of diabetes [79].

Questionnaire-based surveys reported that physical activity could reduce the risk of symptomatic gallstones by one-third [60, 74, 79-81]. Conversely, overnutrition and physical inactivity are the main factors which lead to a high risk of

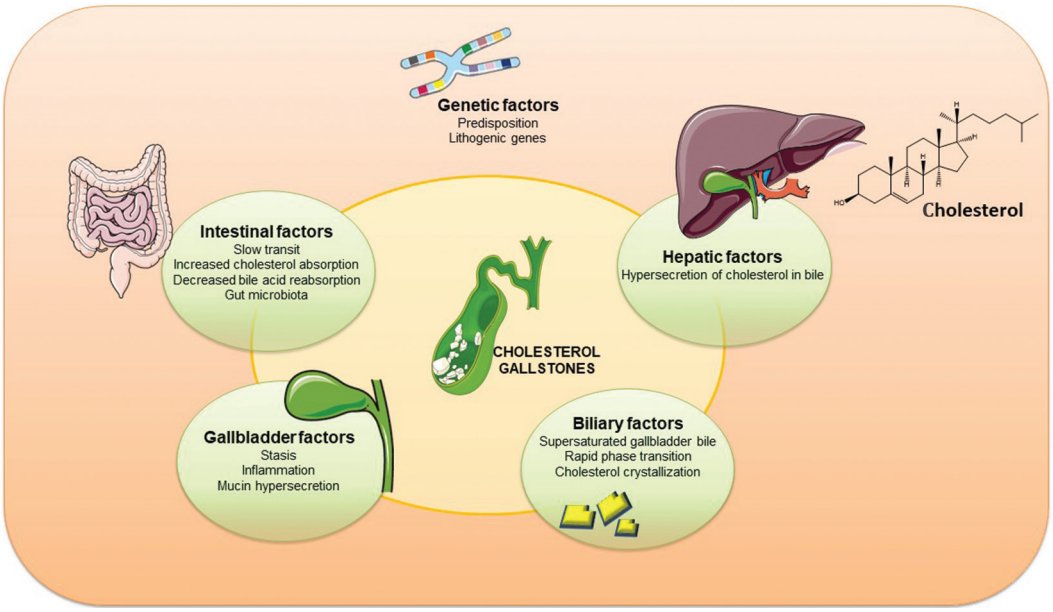

Fig. 1. Pathogenetic factors involved in the formation of cholesterol gallstones. Current research is focusing on several overlapping pathways, and the preeminent role of cholesterol across such pathways is depicted by the chemical formula: - genetic factors (i.e., polygenic predisposition or role of specific lithogenic genes); - hepatic factors (i.e., mainly hypersecretion of biliary cholesterol); - biliary factors (i.e., supersaturated gallbladder bile due to re-absorption of water from the gallbladder epithelium, propensity to transition of liquid micellar cholesterol to concentrated vesicular cholesterol, precipitation of excess cholesterol into solid anhydrous/monohydrate crystals which aggregate and form the first nucleus of cholesterol gallstones); - gallbladder factors (i.e., hypomotile viscus predisposing to stasis of supersaturated, mucin-enriched bile in a chronically inflamed gallbladder); intestinal factors (i.e., sluggish intestine predisposing to increased absorption of dietary and re-circulating biliary cholesterol, decreased bile acid reabsorption and effect of intestinal, mainly colonic microbiota, on biotransformation of primary bile acids into secondary –more lithogenic- bile acids). Adapted from [10, 27, 40, 43, 44, 70, 122, 150-157].

Table II. Main beneficial effects of physical activity on gallbladder by population studies

Study groups	Country	Physical activity recording	Outcomes	Reference
European Prospective Investigation of Cancer (EPIC-Norfolk) Study. 25,639 volunteers, aged 40-74 years monitored over 14 years	UK	Questionnaire (classification of physical activity into four types)	After 5 years of follow-up, 135 participants (69.6% women) developed symptomatic gallstones. 70% decreased risk of gallstones with the highest level of physical activity, compared with the lowest three levels.	[85]
Population-based cohort of 3,143 men and women, 45-74 yr of age, from 13 American Indian communities monitored at baseline (1989-1992) and at follow-up (1993-1995)	USA	Questionnaire (METs/week)	Out of the 2,130 gallstone-free subjects, 650 individuals (403 women and 247 men) developed gallbladder disease according to ultrasound or had cholecystectomy. Increased activity levels were inversely related to gallbladder disease status, and in patients without diabetes.	[79]
Study of Osteoporotic Fractures (SOF; 1986-1988), 8,010 post-menopausal women	USA	Harvard Alumni Questionnaire (kcal/week)	Women in the lowest two quartiles of physical activity had a 59% and a 57% higher risk of developing gallstone disease compared to women in the highest quartile of physical activity. Physical activity inversely related to the development of gallstone disease in post-menopausal women independent of body mass index.	[80]
Ultrasonographic study: 100 subjects with gallstones vs. 290 randomly selected control subjects	Italy	Questionnaire (MJ/week)	Physical activity inversely associated with risk of gallstone formation.	[75]
Prospective cohort study: 45,813 men 40 to 75 years of age were followed from 1986 to 1994.	USA	Questionnaire (METs/week)	828 men with symptomatic gallstones (ultrasonography, radiology, cholecystectomy). Increased physical activity was inversely related to risk for symptomatic gallstone disease.	[74]

Abbreviations: kcal: kilocalories; METs: metabolic equivalent tasks; MJ: megajoules.

CVD, and are major precursors of increased BMI and hepatic cholesterol synthesis rate [33]. Metabolically-active visceral fat deposition, moreover, increases gastrointestinal morbidity and mortality due to gallstone disease, tumors, and endoscopy complications [82]. Low levels of physical activity and serum cholesterol levels represent risk factors for gallbladder disease. The increase in serum HDL levels are inversely associated with gallstone prevalence [29], and regular exercise promotes this increase [23, 24]. Notably, physical activity decreases the risk of cholesterol gallstone formation independently of weight loss, also by improving several metabolic abnormalities such as hyperinsulinemia, high plasma triglycerides and low serum HDL [74].

In a multiethnic large cohort study including non-Hispanic White, African American, Japanese, Native Hawaiian, and Latino followed for a median of 10.7 years, the authors identified 13,437 cases with gallstone disease. Expected and significant risk factors across ethnic/racial populations were BMI over 25 kg/m^2, diabetes, past and current smoking, red meat consumption, saturated fat and cholesterol. Protective factors included vigorous physical activity and consumption of fruits, vegetables and foods rich in dietary fiber. Carbohydrates were inversely associated with gallbladder disease risk only among women and Latinos born in South America/Mexico, while parity was a significant risk factor among women. Postmenopausal hormones use increased the risk among non-Hispanic White women [83].

In line with previous studies, sedentary physical activity has been directly related with hospital admission for gallbladder disease [84]. Using an internationally validated questionnaire, the European Prospective Investigation into Cancer (EPIC-Norfolk study) [85] investigated 25,639 volunteers (aged 40–74 years) for symptomatic gallstones. After 5 and 14 years, four groups of physical activity were examined. The risk of symptomatic gallstones was reduced by 70% in both sexes, with the highest association found in individuals exercising for 1 hour a day in a sedentary job, or 30 minutes a day in a standing job, or doing heavy manual job without any additional activity. The study suggests a causal protective effect of physical activity.

In a prospective study of 7,831 men with 471 incident cases of gallbladder disease (i.e. symptomatic gallstones), decreased physical activity, high BMI, cigarette smoking, and higher diastolic blood pressure increased the risk for clinical gallbladder disease [86]. Dyslipidemia is frequent in gallstone patients, who often have lower serum HDL and higher triglycerides levels, as compared to healthy control subjects [87]. A prior study involving inactive persons, marathoners and joggers found that physical activity levels were inversely associated with serum triglycerides [88]. Petitti et al. [29] reported that gallstone disease prevalence correlated positively to total, serum LDL/very low-density lipoprotein (VLDL) levels and triglycerides, and inversely to serum HDL levels. Thus, increasing physical activity can also be beneficial to cholelithiasis by lowering serum triglycerides [86], as well as other manifestations of dyslipidemia.

Hyperinsulinemia, a major component of the metabolic syndrome, promotes hepatic cholesterol uptake [89]. This condition, in turn, increases the secretion of biliary cholesterol [90], while reducing the secretion of bile acids (BA) [91]. These conditions predispose to the accumulation of cholesterol in

bile, creating a supersaturated environment with excess of cholesterol [10, 92]. By contrast, regular exercise decreases insulin levels [93], as well as insulin resistance [94]. Physical activity also appears to stimulate hormonal mechanisms, such as the cholecystokinin-dependent gallbladder contraction [95], with a prokinetic effect on the intestine [96]. In this way, a regular program of physical activity would intercept and bring benefits on several pathogenic factors of (cholesterol) cholelithiasis.

In order to prevent gallstone disease and metabolic disorders [6, 13, 97], keeping the ideal body weight is more important than losing excess of weight, as part of healthy lifestyles. Rapid weight loss, in fact, can lead to opposite effects. One third of these subjects have increased risk of gallstone formation due to rapid mobilization of body cholesterol and increased secretion in bile [33]. Therefore, the rapidity of weight loss, as well as the degree of obesity, are crucial in gallstones development [98]. In symptomatic gallstone patients, exercise may reduce pain perception, with mechanisms probably involving gallbladder motility and bile secretion [99].

Physical activity could also lead to a better health-related quality of life (HRQoL) in patients with gallstone disease [100, 101]. Physical activity may imply less discomfort and reduced pain, as reported in several cohorts [102, 103]. Of note, patients with gallstone disease generally report decreased physical function and increased bodily pain [104, 105]. Several aspects in HRQoL, such as bodily pain or physical function, can improve postoperatively [106]. However, more studies are needed to better explore HRQoL outcomes in gallbladder patients [107]. Similar to the improvements observed in HRQoL after laparoscopic cholecystectomy [108], more clinical trials assessing the effect of physical activity in HRQoL should be considered in gallbladder disease.

The results of a systematic review and meta-analysis [109] based on eight selected studies [60, 74, 80, 85, 86, 110-112] confirm that high levels of physical activity reduce the risk of gallbladder disease. Further studies also support that vigorous physical activity is inversely associated with risk of gallbladder disease [83], and reduces the risk of cholecystectomy [113]. Higher levels of physical activity (above 16.6 METs/hour per week in males or 10.2 METs/hourper week in females) are able to reduce the occurrence of symptoms [59, 60]. Vigorous physical activity protected against cholecystectomy in adult women [114]. Likewise, as reported in a five-year long study, higher levels of physical activity might be associated with a reduction of the risk for symptomatic gallstones by 70% [85]. Further research is necessary in this field, looking at the effects of dose-response relationship between physical activity and specific types of physical activity and pathophysiologic mechanisms leading to gallstones symptoms and complications in gallbladder disease, as well as in different populations. More objective measurements such as accelerometers might help in this respect [79].

Aerobic capacity plays a role with respect to gallstone disease. An increased aerobic capacity level is linked with a decreased prevalence of gallbladder disease [110, 115]. A protective role exists for both asymptomatic [114] or symptomatic (70% risk reduction [85]) gallstone development, for gallbladder disease [109], and potentially for gallbladder cancer [116]. An increase in aerobic capacity of one MET reduces the odds of suffering from gallbladder disease by 8% in men and by 13% in women, respectively [115]. As mentioned earlier, vigorous aerobic physical activity is inversely associated with gallbladder risk, as measured by aerobic capacity [110]. Hospital admissions for gallbladder disease also appear to be inversely associated to physical activity [84, 117]. Remarkably, frequent aerobic exercise may favorably influence the progression of both gallbladder cancer and gallstones formation [116].

Physical activity is also able to modulate gastrointestinal motility [118, 119], by affecting the release of cholecystokinin (CCK), the pro-kinetic hormone [99, 120]. The effects on CCK are also able to influence hunger (i.e. suppressing action), as shown in a study exploring acute aerobic physical activity (from 30 to 120 min) [121]. One aspect to consider with respect to physical activity and gastrointestinal tract is the ongoing recirculation of BA within the enterohepatic circulation. Bile acids contribute to lipid components in bile, together with cholesterol and phospholipids. In the hepatocyte, primary BA are cholic acid and chenodeoxycholic acid, synthetized from cholesterol. Both BA are conjugated to taurine and glycine to increase their solubility in bile (Fig. 2A and 2B). Following secretion into the biliary tract, BA progressing to the terminal ileum and colon are bio-transformed into secondary BA (deoxycholic acid, litocholic acid) and tertiary BA (ursodeoxycholic acid) (Figure 2A) by the resident colonic microbiota. Approximately 95% of conjugated BA are re-absorbed (actively in the terminal ileum mainly, and about 15% passively in the colon) and return to the liver via the portal vein across the enterohepatic circulation [122]. Bile acids represent amphiphilic molecules which contribute to digestion and absorption of fat, cholesterol, and fat-soluble vitamins. Bile acids also act as signaling (hormonal) molecules and display antimicrobial and anti-inflammatory functions [122]. Thus, the study of the effects of physical activity on human body should also take into account the consequences in the enterohepatic circulation of BA. Prior animals studies show that moderate physical activity may increase BA excretion [123-125]. In turn, BA would activate the small intestinal farnesoid X receptor (FXR) with increased expression of the human enterokine fibroblast growth factor 19 (FGF19). This interaction results in activation of the FGF4 receptor/β-clotho in the liver and small heterodimer-mediated inhibition of BA synthesis [122, 126], because of the reduced expression of hepatic cholesterol 7α-hydroxylase and BA synthesis [127]. In a mice study, however, BA secretion and fecal output increased after physical activity but the mechanism was increased with reverse cholesterol transport, independently from upregulation of genes involved in BA synthesis and FXR-FGF15 (FGF19 in humans) feedback [128]. In runners, both fecal and serum BA concentrations were decreased [129, 130], with decreased mutagenic secondary BA [130].

In the small intestine and in the liver, BA also activate another epithelial receptor, i.e., the G protein bile acid receptor 1 (GPBAR-1) [131, 132]. This activation releases hormones such as peptide YY (PYY) with anorexigenic effect (i.e., appetite reduction) and glucagon-like peptides (GLP-1 and GLP-2) which produce effects in the glucose and insulin metabolism

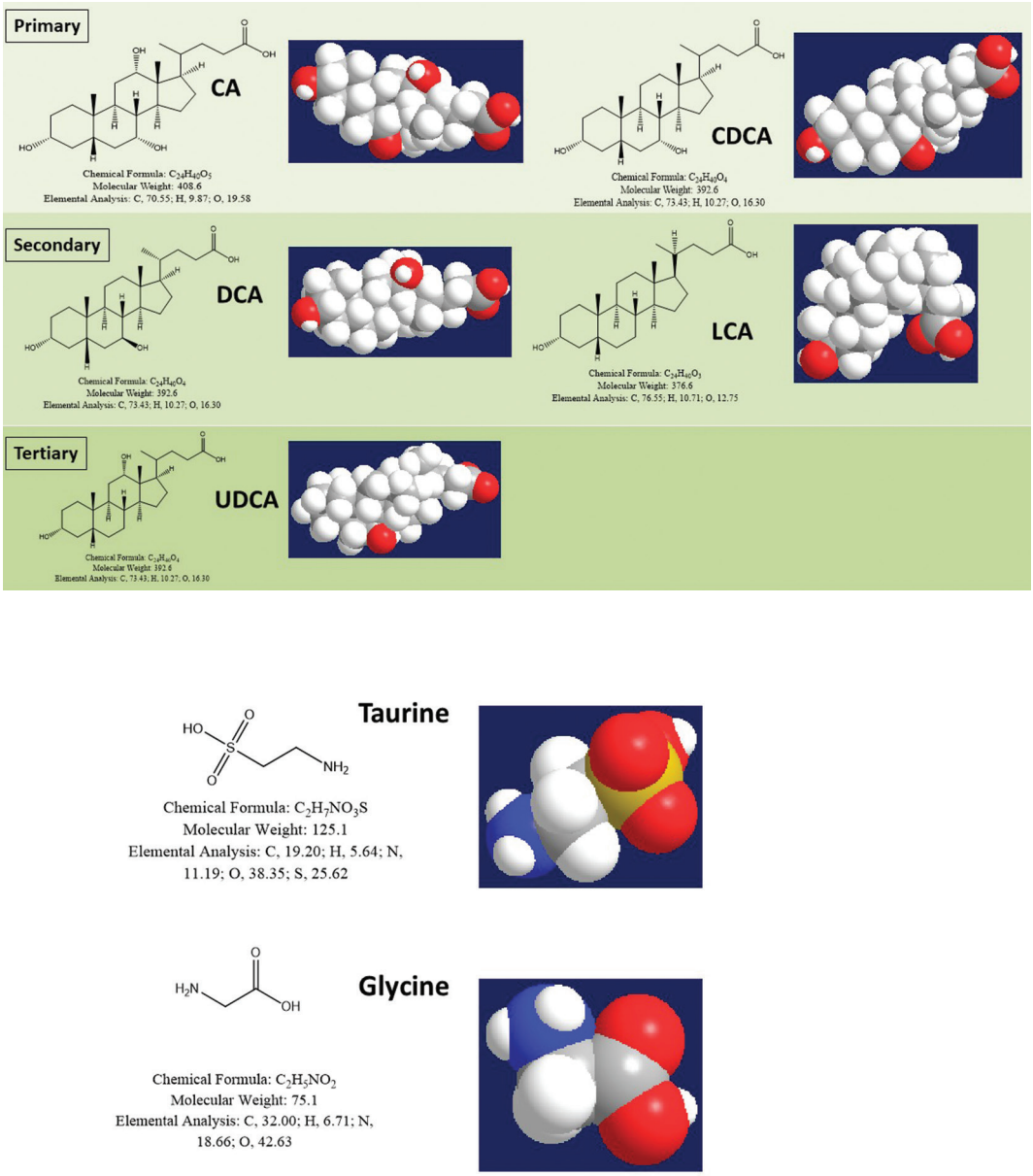

Fig. 2. A. Structure, chemical formula, molecular weight, elemental analysis and 3D formula of human bile acids. Primary bile acids are cholic acid (CA) and chenodeoxycholic acid (CDCA). Secondary bile acids are deoxycholic acid (DCA) and lithocholic acid (LCA). Tertiary bile acid is ursodeoxycholic acid (UDCA). **B**. Structure, chemical formula, molecular weight, elemental analysis and 3D formula of taurine and glycine which upon conjugation with bile acids increase their solubilization in bile.

[133]. GPBAR-1 localizes also in the gallbladder, brown adipose tissue, skeletal muscle, macrophages, and monocytes [126, 132], and in the enteroendocrine cells of the intestine [122, 134, 135]. In the skeletal muscle and brown adipose tissue, GPBAR-1 signaling leads to local activation of the type II iodothyronine deiodinase (DIO2), which transforms the inactive thyroxine (T4) to active thyroid hormone (T3, a key regulator of metabolism and energy homeostasis). In Kupffer cells and macrophages, GPBAR-1 activation inhibits Lipopolysaccharide (LPS)-induced cytokine production [136]. Such additional hormonal effects of BA are cAMP-mediated and might be particularly evident after bariatric surgery with important and beneficial metabolic effects, including increased energy expenditure, increased insulin secretion and/or sensitivity and decreased inflammatory status [127, 136, 137].

Physical activity may also produce anti-inflammatory effects in the body. These anti-inflammatory effects could be promoted by GPBAR-1 activation, which is induced by circulating BA in the liver Kupffer cells [138]. Physical activity might partially mediate this effect [139, 140]. Further, several anti-inflammatory changes are followed by BA-induced activation of GPBAR-1, which can be observed in other immune cells such as macrophages, monocytes, and dendritic cells [141]. These changes potentially induce further inhibition of NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome, which are protective against lipopolysaccharide-induced inflammation and atherosclerosis [142]. The additional anti-inflammatory effects might be induced by changes in gut microbiota induced by physical exercise [143]. In the enterohepatic circulation,

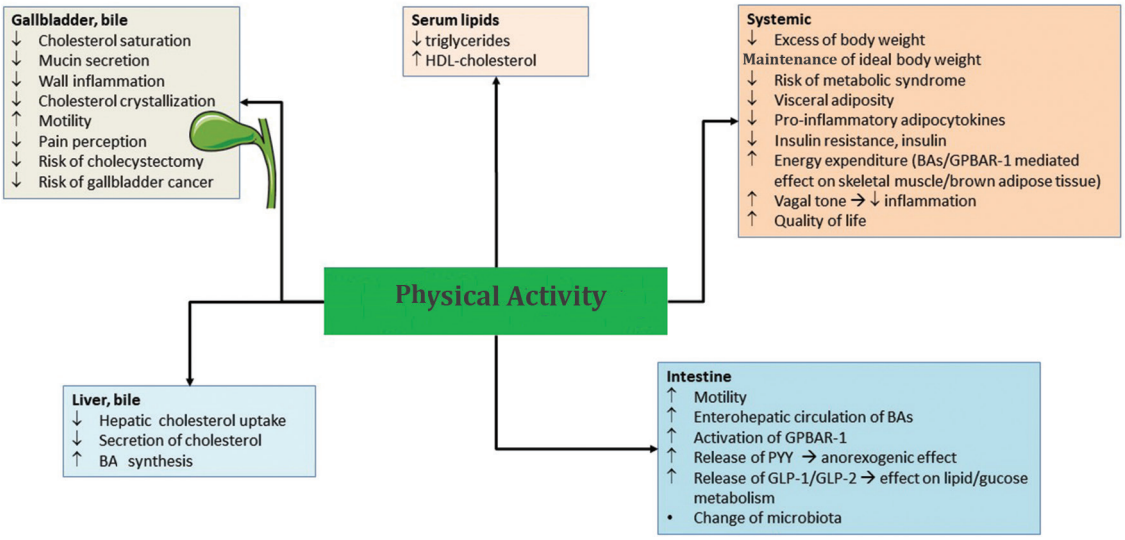

Fig. 3. Summary of the effects of physical activity on the gallbladder, and outside the gallbladder. With respect to cholelithiasis, beneficial effects can therefore activate either direct and/or indirect pathways.
Abbreviations: BA: bile acids; GLP-1/2: glucagon-like peptide 1/2; GPBAR-1: G protein bile acid receptor 1; PYY: peptide YY; ↑: increased; ↓: decreased. Image found on https://wallpapersafari.com/w/0O9mLa.

gut microbiota during physical exercise may also activate additional anti-inflammatory effects. The interaction of gut microbiota with BA in the enterohepatic circulation leads to the conversion of primary to secondary BA which, in turn, influence gut microbiota by exerting antimicrobial effects [144]. Ursodeoxycholic acid and lithocholic acid were recently shown to have anti-inflammatory properties by decreasing the release of pro-inflammatory cytokines while increasing the macrophage release of anti-inflammatory cytokines [144].

Furthermore, vagal tone is increased by regular physical activity [145, 146], which also decreases the expression of inflammatory markers [146]. However, studies have recently shown contradictory results, while others [147, 148] speculate a decrease in circulatory apoptosis to be correlated to increased aerobic capacity [149]. Also, gallbladder emptying, as mediated by vagal tone, could be a response of a neuro-hormonal product of physical exercise [95, 116].

CONCLUSIONS

Physical activity is an integral part of healthy lifestyles, contributing to the maintenance of ideal weight and, thus, counteracting the increasing burden of non-communicable diseases and metabolic abnormalities related to obesity and sedentary behaviors. The beneficial effects of regular physical activity on cardiovascular and metabolic disorders are well established. Aerobic physical activity also brings beneficial effects on the biliary tract, which include the prevention of gallstones, the decrease of gallstone-related symptoms and complications, as well as rate of hospitalization and a better quality of life. The beneficial effects of regular physical activity intercept several pathways, which go far beyond the direct effects on the gallbladder (i.e., improved kinetics and eased local inflammatory changes, decreased precipitation of crystallized cholesterol in the hypomotile viscus). More systemic anti-lithogenic effects of physical activity involve lipid metabolism, intestinal motility, insulin resistance, enterohepatic circulation of BA and their hormone-mediated energy expenditure, maintenance of body weight or decrease of excess body weight and, therefore, decreased impact of dysmetabolic pro-lithogenic factors (Fig. 3).

Thus, regular physical activity, as part of an overall healthy lifestyle plan, represents a plus for primary and secondary prevention of gallbladder disease, by the involvement of end-organ and systemic mechanisms.

Further studies should better explore distinctive outcomes of modality and intensity of physical activity, the harmful and beneficial effects of physical activity in populations of different ages and ethnicity, in different metabolic abnormalities, and in subjects exposed to different nutritional intake and environmental changes.

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